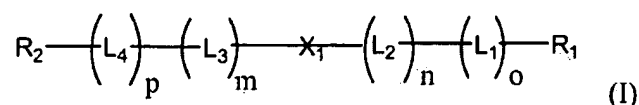


**AMENDMENTS TO THE CLAIMS**

This listing of claims will replace all prior versions, and listings, of claims in the application.

## Listing of Claims:

1. (Currently Amended) An oligonucleotide prodrug of the formula (I):



wherein:

R<sub>1</sub> is and R<sub>2</sub> are independently H or a polymer residue;

R<sub>2</sub> is H;

L<sub>1</sub> and L<sub>4</sub> are independently selected releasable linking moieties;

L<sub>2</sub> and L<sub>3</sub> are independently selected bifunctional spacing groups each comprising from about 2 to about 10 carbon atoms;

X<sub>1</sub> is a single or double stranded oligonucleotide residue wherein the oligonucleotide ranges in size from 10 to 1,000 nucleotides;

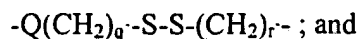
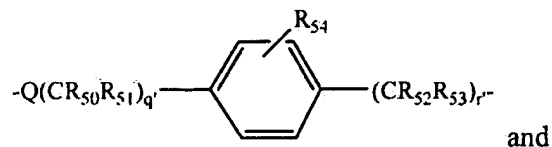
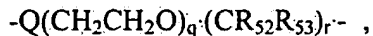
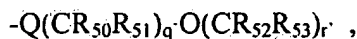
m, n, and o are independently zero or a positive integer; and

m and p are zero,

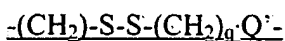
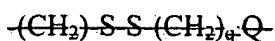
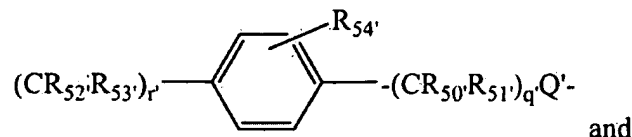
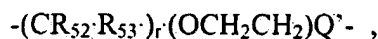
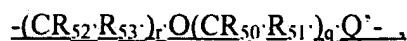
provided that either (o + n) or (p + m) ≥ 2; and

wherein

L<sub>3</sub> is selected from the group consisting of:



$L_2$  is selected from the group consisting of:



wherein  $[[.]]$

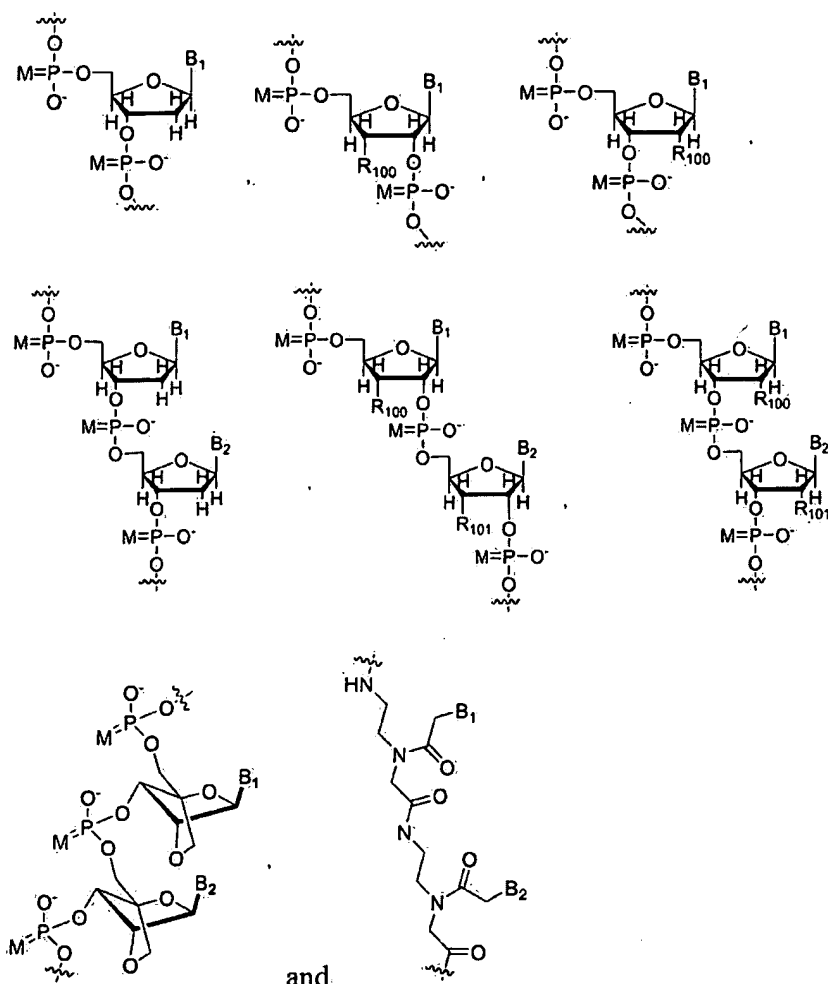
$Q$  and  $Q'$  are independently selected from O, S or NH;

$R_{50-53}$  and  $R_{50'-53'}$  are independently selected from the group consisting of hydrogen,  $C_{1-6}$  alkyls,  $C_{3-12}$  branched alkyls,  $C_{3-8}$  cycloalkyls,  $C_{1-6}$  substituted alkyls,  $C_{3-8}$  substituted cycloalkyls, aryls substituted aryls, aralkyls,  $C_{1-6}$  heteroalkyls, substituted  $C_{1-6}$  heteroalkyls,  $C_{1-6}$  alkoxy, phenoxy and  $C_{1-6}$  heteroalkoxy;

$R_{54}$  and  $R_{54'}$  are independently selected from the group consisting of hydrogen,  $C_{1-6}$  alkyls,  $C_{3-12}$  branched alkyls,  $C_{3-8}$  cycloalkyls,  $C_{1-6}$  substituted alkyls,  $C_{3-8}$  substituted cycloalkyls, aryls substituted aryls, aralkyls,  $C_{1-6}$  heteroalkyls, substituted  $C_{1-6}$  heteroalkyls,  $C_{1-6}$  alkoxy, phenoxy,  $C_{1-6}$  heteroalkoxy,  $NO_2$ , haloalkyl and halogen; and

$q'$  and  $r'$  are each a positive integer.

2. (Currently Amended) The prodrug of claim 27 ~~+~~, wherein the oligonucleotide comprises a nucleotide that is selected from the group consisting of



and

wherein

M is O or S;

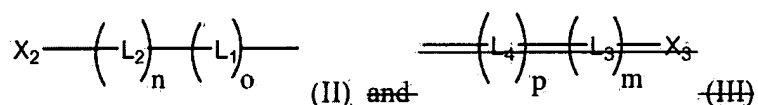
B<sub>1</sub> and B<sub>2</sub> are independently selected from the group consisting of A (adenine), G (guanine), C (cytosine), T (thymine), U (uracil) and modified bases;

R<sub>100</sub> and R<sub>101</sub> are independently selected from the group consisting of H, OR' where R' is H, a C<sub>1-6</sub> alkyl, substituted alkyls, nitro, halo and aryl

3. (Currently Amended) The prodrug of claim 274, wherein said oligonucleotide contains from about 10 to about 1000 nucleotides.

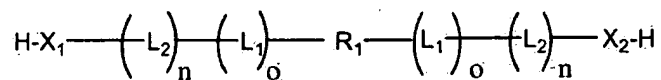
4. (Previously Presented) The prodrug of claim 2, wherein M is S.

5. (Currently Amended) The prodrug of claim 27 ~~+~~, wherein the oligonucleotide residue is a phosphorothioate oligonucleotide residue.
6. (Currently Amended) The prodrug of claim 27 ~~+~~, wherein said oligonucleotide residue is an antisense oligonucleotide residue or oligodeoxynucleotide residue.
7. (Previously Presented) The prodrug of claim 6, wherein said antisense oligonucleotide residue or oligodeoxynucleotide residue is selected from the group consisting of, oligonucleotides and oligodeoxynucleotides with phosphodiester backbones or phosphorothioate backbones, LNA, PNA, tricyclo-DNA, decoy ODN, ribozymes, siRNAs, and CpG oligomers.
8. (Currently Amended) The prodrug of claim 6, wherein said antisense oligonucleotide has a sequence selected from the group consisting of SEQ ID NO: 1, SEQ ID NO: 2, SEQ ID NO: 3, and SEQ ID NO: 4, wherein n of SEQ ID NO: 4 is any ~~compatible~~ nucleotide.
9. (Currently Amended) The prodrug of claim 27 ~~+~~, wherein ~~at least one of~~  $R_1$  and  $R_2$  is a polymeric residue having a capping group A, selected from the group consisting of OH,  $NH_2$ , SH,  $CO_2H$ ,  $C_{1-6}$  alkyls, and

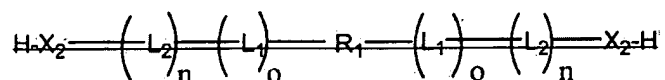


wherein  $X_2$  is a single stranded or double stranded ~~and~~  $X_3$  are independently selected nucleotide or oligonucleotide residues, wherein the oligonucleotide ranges in size from 10 to 1,000 nucleotides.

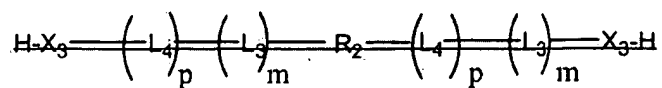
10. (Currently Amended) A prodrug of claim 9, selected from the group consisting of:



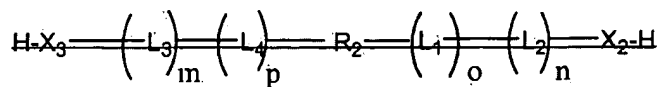
wherein each  $X_2$  is independently 3' oligonucleotide or 5' oligonucleotide.



~~(i) bis-3'-oligonucleotide;~~

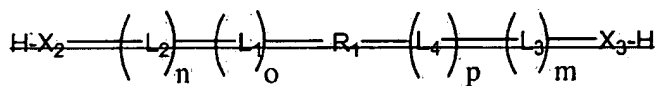


~~(ii) bis-5'-oligonucleotide;~~



~~(iii) bis-5', 3'-oligonucleotide;~~

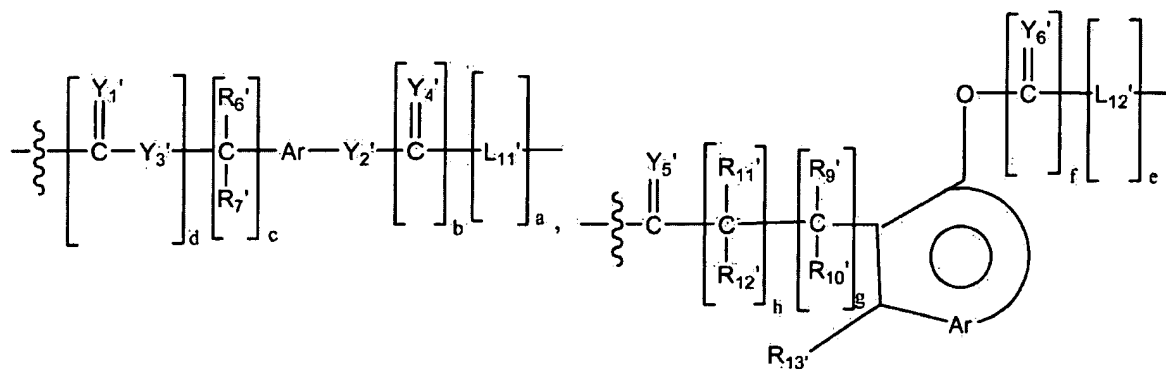
and

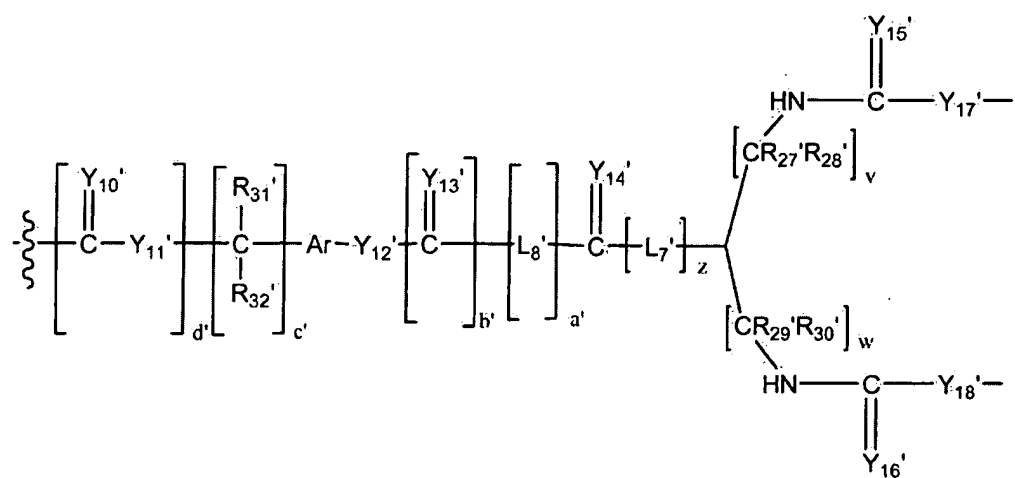
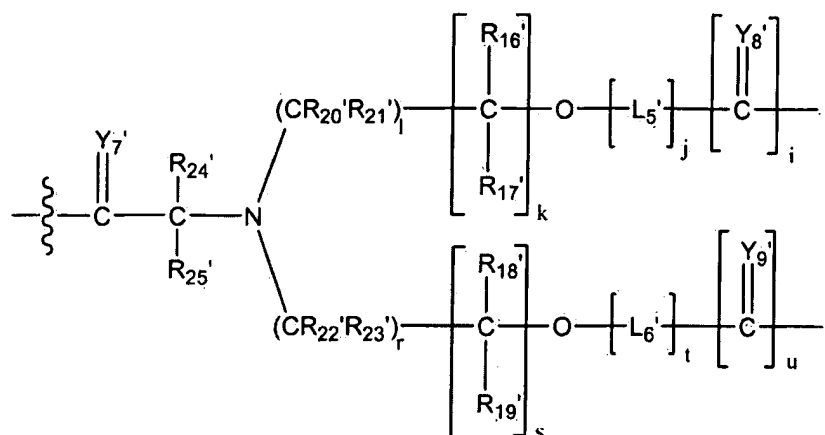


~~(iv) bis-3', 5'-oligonucleotide.~~

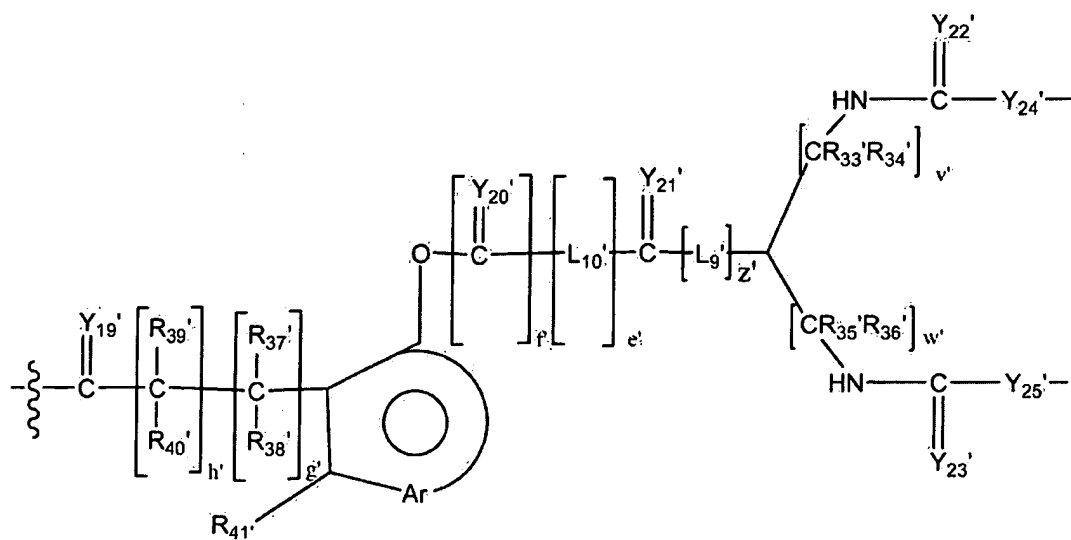
11. (Cancelled)

12. (Currently Amended) The prodrug of claim 27, ~~4~~ wherein  $L_1$  is selected from the group consisting of:





and



wherein,

$Y_1$ ,  $Y_{25}$  are independently selected from the group consisting of O, S or  $NR_9$ ;

$R_{6-7}$ ,  $R_{9-13}$ ,  $R_{16-25}$ ,  $R_9$  and  $R_{27-41}$  are independently selected from the group consisting of hydrogen,  $C_{1-6}$  alkyls,  $C_{3-12}$  branched alkyls,  $C_{3-8}$  cycloalkyls,  $C_{1-6}$  substituted alkyls,  $C_{3-8}$  substituted cycloalkyls, aryls, substituted aryls, aralkyls,  $C_{1-6}$  heteroalkyls, substituted  $C_{1-6}$  heteroalkyls,  $C_{1-6}$  alkoxy, phenoxy and  $C_{1-6}$  heteroalkoxy; and

$L_{5-12}$  are independently selected bifunctional spacers;

Ar is a moiety which forms a multi-substituted aromatic hydrocarbon or a multi-substituted heterocyclic group;

c, h, k, l, r, s, v, w,  $v'$ ,  $w'$ ,  $c'$ , and  $h'$  are independently selected positive integers;

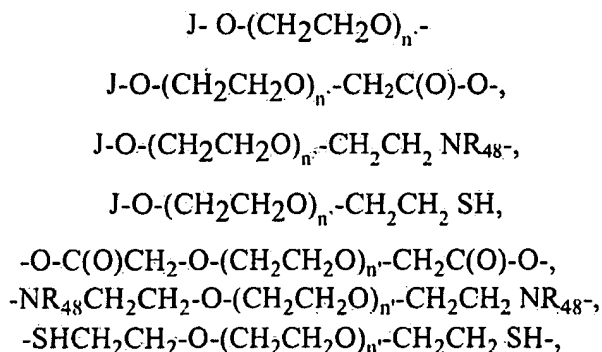
a, e, g, j, t, z,  $a'$ ,  $z'$ ,  $e'$  and  $g'$  are independently either zero or a positive integer; and

b, d, f, i, u,  $b'$ ,  $d'$  and  $f'$  are independently zero or one.

13. (Currently Amended) The prodrug of claim 27, ~~+~~ wherein  $R_1$  is a polyalkylene oxide  ~~$R_{1-2}$  are each polyalkylene oxides.~~

14. (Currently Amended) The prodrug of claim 27, ~~+~~ wherein  $R_1$  is a polyalkylene glycol  ~~$R_{1-2}$  are each polyethylene glycols.~~

15. (Currently Amended) The prodrug of claim 27, ~~+~~ wherein  ~~$R_{1-2}$  are independently~~  $R_1$  is selected from the group consisting of:



wherein

$n'$  is the degree of polymerization;

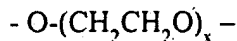
$R_{48}$  is selected from the group consisting of hydrogen,  $C_{1-6}$  alkyls,

$C_{3-12}$  branched alkyls,  $C_{3-8}$  cycloalkyls,  $C_{1-6}$  substituted alkyls,  $C_{3-8}$  substituted cycloalkyls,

aryls substituted aryls, aralkyls, C<sub>1-6</sub> heteroalkyls, substituted C<sub>1-6</sub>heteroalkyls, C<sub>1-6</sub>alkoxy, phenoxy and C<sub>1-6</sub> heteroalkoxy; and

J is a capping group.

16. (Currently Amended) The prodrug of claim 27 ~~+~~, wherein ~~R<sub>1-2</sub> are independently~~ R<sub>1</sub> comprises



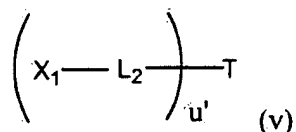
wherein x is a positive integer selected so that the weight average molecular weight is at least about 2,000 Da to about 136,000 Da.

17. (Currently Amended) The prodrug of claim 27 ~~+~~, wherein ~~R<sub>1-2</sub> independently have~~ R<sub>1</sub> has a weight average molecular weight of from about 3,000 Da to about 100,000 Da.

18. (Currently Amended) The prodrug of claim 27 ~~+~~, wherein ~~R<sub>1-2</sub> independently have~~ R<sub>1</sub> has a weight average molecular weight of from about 5,000 Da to about 40,000 Da.

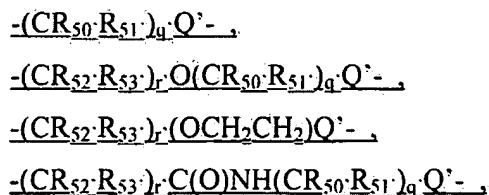
19. (Previously Presented) The prodrug of claim 8, wherein said antisense oligonucleotide is oblimersen (SEQ ID NO: 1).

20. (Withdrawn/Currently Amended) An oligonucleotide prodrug of the formula:

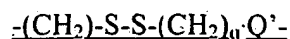
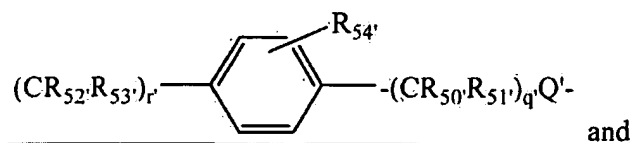


wherein:

~~L<sub>2</sub> is a spacing group~~ selected from the group consisting of:







wherein

each Q' is independently selected from O, S or NH;

$\text{R}_{50-53}$  are independently selected from the group consisting of hydrogen,  $\text{C}_{1-6}$  alkyls,  $\text{C}_{3-12}$  branched alkyls,  $\text{C}_{3-8}$  cycloalkyls,  $\text{C}_{1-6}$  substituted alkyls,  $\text{C}_{3-8}$  substituted cycloalkyls, aryls substituted aryls, aralkyls,  $\text{C}_{1-6}$  heteroalkyls, substituted  $\text{C}_{1-6}$  heteroalkyls,  $\text{C}_{1-6}$  alkoxy, phenoxy and  $\text{C}_{1-6}$  heteroalkoxy;

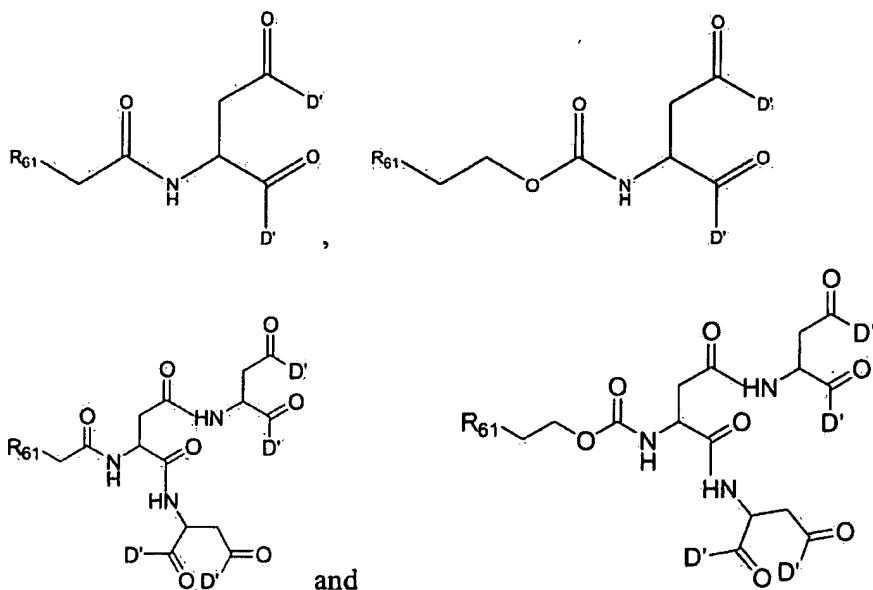
$\text{R}_{54}$  is independently selected from the group consisting of hydrogen,  $\text{C}_{1-6}$  alkyls,  $\text{C}_{3-12}$  branched alkyls,  $\text{C}_{3-8}$  cycloalkyls,  $\text{C}_{1-6}$  substituted alkyls,  $\text{C}_{3-8}$  substituted cycloalkyls, aryls substituted aryls, aralkyls,  $\text{C}_{1-6}$  heteroalkyls, substituted  $\text{C}_{1-6}$  heteroalkyls,  $\text{C}_{1-6}$  alkoxy, phenoxy,  $\text{C}_{1-6}$  heteroalkoxy,  $\text{NO}_2$ , haloalkyl and halogen; and

$q$  and  $r$  are each a positive integer;

$\text{X}_1$  is a nucleotide or an single or double stranded oligonucleotide residue wherein the oligonucleotide ranges in size from 10 to 1,000 nucleotides;

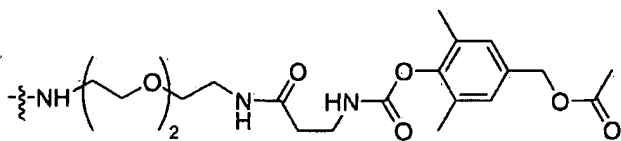
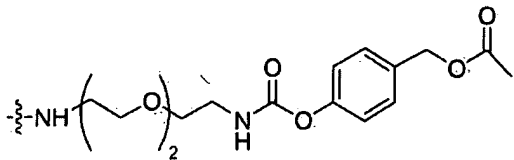
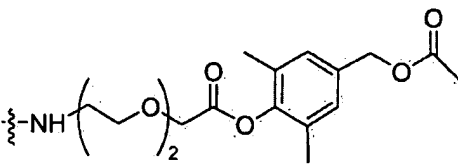
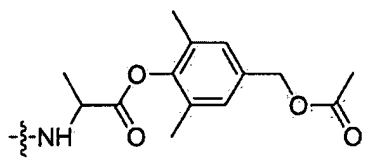
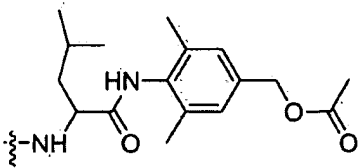
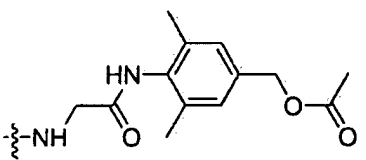
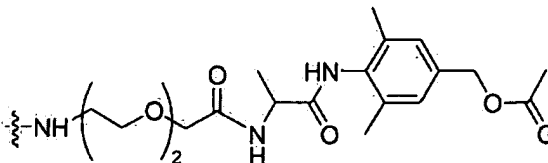
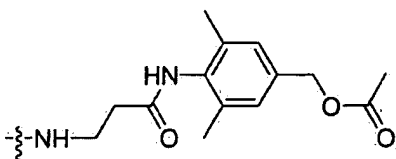
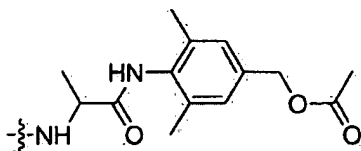
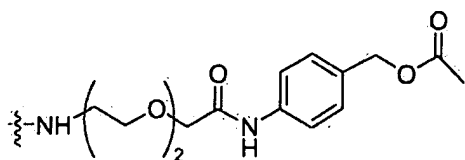
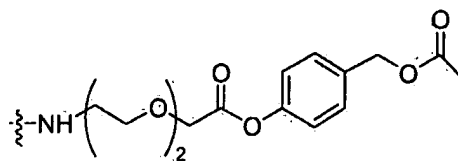
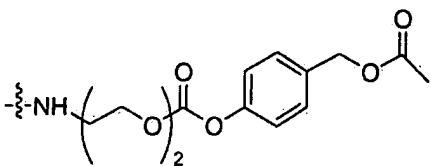
$u$  is a positive integer; and

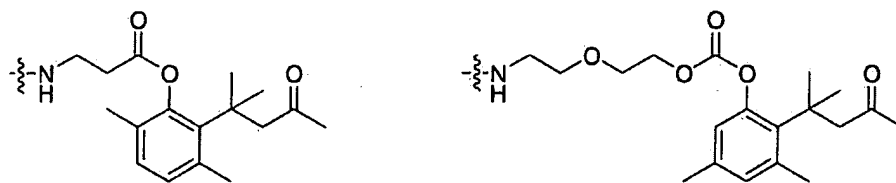
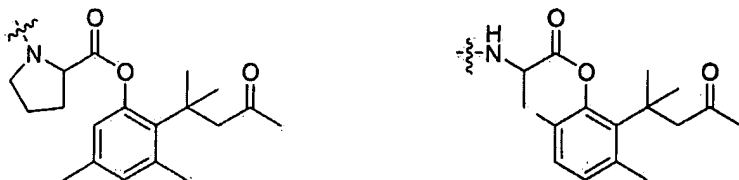
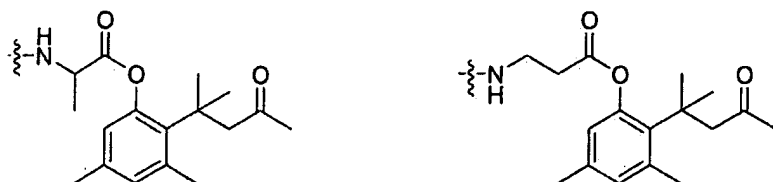
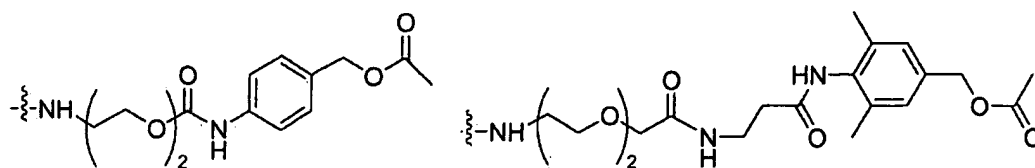
T is a member of the group consisting of:



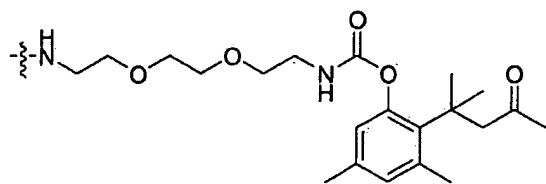
wherein:

D' is one of



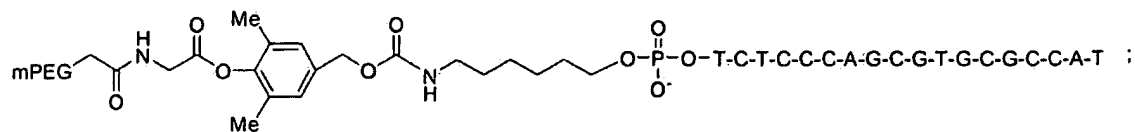


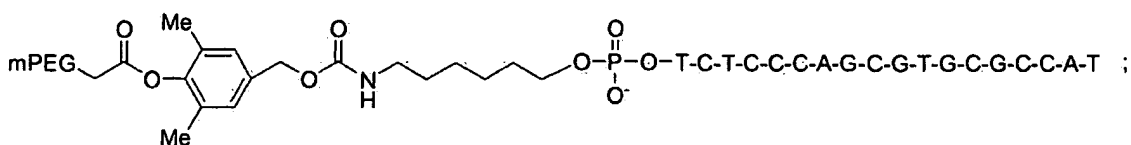
and



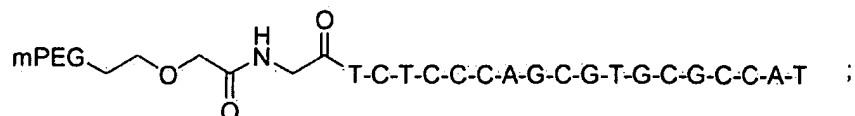
and wherein  $R_{61}$  is a polymer residue.

21. (Currently Amended) The prodrug of claim 27 + selected from the group consisting of:





and



all of which comprise an oligonucleotide of SEQ ID NO: 1.

22. (Currently Amended/Withdrawn) A method of making a prodrug comprising:  
reacting a compound of the formula:

R<sub>1</sub>-L<sub>1</sub>-leaving group

R<sub>2</sub>-L<sub>4</sub>-leaving group

with a compound of the formula:

H-L<sub>2</sub>-X<sub>1</sub>

H-L<sub>3</sub>-X<sub>1</sub>

under conditions sufficient to form a prodrug of the formula

R<sub>1</sub>-L<sub>1</sub>-L<sub>2</sub>-X<sub>1</sub>,

R<sub>2</sub>-L<sub>4</sub>-L<sub>3</sub>-X<sub>1</sub>,

wherein:

R<sub>2</sub> R<sub>1</sub> is a polymer residue;

L<sub>4</sub> L<sub>1</sub> is a releasable linking moiety;

L<sub>3</sub> L<sub>2</sub> is a bifunctional spacing group comprising from about 2 to about 10 carbon atoms;

and

X<sub>1</sub> is a single or double stranded nucleotide or an oligonucleotide residue wherein the oligonucleotide ranges in size from 10 to 1,000 nucleotides.

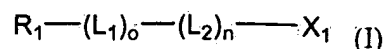
23. (Currently Amended/Withdrawn) A method of treating a mammal, comprising administering to a mammal in need of such treatment an effective amount of a compound of claim 27 +.

24. (Withdrawn) The method of claim 23, wherein the mammal is being treated for cancer.

25. (Withdrawn) The method of claim 23, wherein  $X_1$  is an antisense oligonucleotide.

26. (Withdrawn) The method of claim 23 wherein the mammal is also treated with a second anticancer agent that is administered simultaneously or sequentially with the oligonucleotide prodrug.

27. (New) An oligonucleotide prodrug of the formula (I):



wherein:

$R_1$  is a polymer residue;

$L_1$  a releasable linking moiety;

$L_2$  is a selected bifunctional spacing group comprising from about 2 to about 10 carbon atoms;

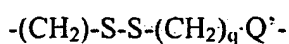
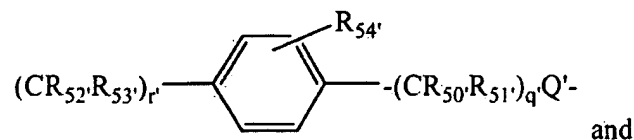
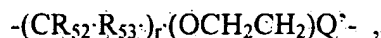
$X_1$  is a single or double stranded oligonucleotide residue wherein the oligonucleotide ranges in size from 10 to 1,000 nucleotides;

$n$ , and  $o$  are independently a positive integer; and

provided that  $(o + n) \geq 2$ ,

wherein

$L_2$  is selected from the group consisting of:



wherein

each  $Q'$  is independently selected from O, S or NH;

$R_{50-53}$  are independently selected from the group consisting of hydrogen,  $C_{1-6}$  alkyls,  $C_{3-12}$  branched alkyls,  $C_{3-8}$  cycloalkyls,  $C_{1-6}$  substituted alkyls,  $C_{3-8}$  substituted cyloalkyls, aryls substituted aryls, aralkyls,  $C_{1-6}$  heteroalkyls, substituted  $C_{1-6}$  heteroalkyls,  $C_{1-6}$  alkoxy, phenoxy and  $C_{1-6}$  heteroalkoxy;

$R_{54}$  is independently selected from the group consisting of hydrogen,  $C_{1-6}$  alkyls,  $C_{3-12}$  branched alkyls,  $C_{3-8}$  cycloalkyls,  $C_{1-6}$  substituted alkyls,  $C_{3-8}$  substituted cyloalkyls, aryls substituted aryls, aralkyls,  $C_{1-6}$  heteroalkyls, substituted  $C_{1-6}$  heteroalkyls,  $C_{1-6}$  alkoxy, phenoxy,  $C_{1-6}$  heteroalkoxy,  $NO_2$ , haloalkyl and halogen; and

$q$  and  $r$  are each a positive integer.